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10/671,883	09/29/2003	Xiaolei Yu	035642-0105	5369

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/26/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,883	YU ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *8 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 6, 2006. Currently, claims 1-7 and 9-10 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

a. The 112/2nd rejection has withdrawn because the amendment and arguments obviate the rejection.

4. This action contains new grounds for rejection necessitated by amendment.

Election/Restrictions

Claim 8 has been withdrawn. In amending claim 8 to contain all the capture probes listed in table I, the claim is no longer drawn to the capture probe E.col-GyA87A1 elected in the restriction response filed on June 5, 2006, because the amended claim requires all of the capture probes of Table I.

Maintained Rejections

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim 4 is drawn to a method for detecting quinolone resistance of E.coli and requires the use of nucleic acid probes with structure R_1- (Y)-R_2, where Y is all the permutations of the triplet at amino acid 87 of the parC protein, for hybridization with a nucleic acid sequence and determination of quinolone resistance based on hybridization. Accordingly, the claim appears to require that certain probes, with specific permutations for codon 87 of parC, will be indicative of resistance to quinolones. However, the specification does not teach what amino acid at position 87 of parC is responsible for quinolone resistance. The claims encompass use of a genus of specific probes, which are indicative of quinolone resistance without actually providing any teaching of any members of the species. At page 9, the specification teaches, "Three amino acids positions, i.e. residues 80, 84, and 87 have been chosen as locations for detection." While the specification taught that such mutations for detection of position 80 include Ile or Arg, and position 84 include Lys or Glu, the specification is silent as to the mutations that need to be detected for position 87 to be indicative of quinolone resistance. There is no teaching of any structure that imparts the particular function claimed.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number"

depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids at residue 87, which are indicative of quinolone resistance. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids, which are indicative of quinolone resistance, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely

based on its functional utility, as a mutation, without any definition of the particular mutation claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

The response traverses the rejection. The response asserts that the claim defines the capture probes by the sequence, R_3-(Y)-R_4, wherein Y designates all permutations of the triplets at amino acid positions 80, 84 or 87 of parC (see page 5 of response October 6, 2006).

This argument has been considered but is not convincing because the formula representing a nucleotide sequence by R in claims 1 and 4 is not a specific sequence, but represents a genus of nucleotides in this case ranging from 5 to 20 nucleotides on each side of Y. As the claim recites, R_3 and R_4 can be from 5 to 20 nucleotides, the capture probes claimed can be from 13 to 43 nucleotides, with 64 possible nucleotide

combinations represented by Y, alone. This is an enormous genus of nucleotides claimed without a specific nucleotide sequence or SEQ ID NO recited in the claim.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3, 5, 6, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weigel et al (WO99/50458) in view of Chee et al (A) (WO 95/11995) and Alberts et al (Molecular biology of the Cell, (1994) Garland Publishing, page 103).

Claim 1 is drawn to obtaining a biological sample, optionally isolating and/or amplifying DNA from the sample and contacting the DNA from the sample with an array

with capture probes derived from the sequence of gyrA gene of E. coli to examine the presence of mutations at nucleotide positions corresponding to amino acids 83 and 87.

With regards to claim 1-3, Wiegel et al teaches determination of mutations of nucleotides in codons 83 and 87 relates to quinolone resistant E coli gyrA (see figures 4a and 4b, and page 18 lines 31-33). Wiegel et al teaches wild type codon ser83 (TCG) and mutant codons Leu (TTG), Thr (ACT), Thr (ACC), (Ser) AGC, Ser (TCC), Ile (ATC), Phe (TTC), Tyr (TAC), Ile (ATT), Arg (CGC), Arg (AGG), Arg (AGA)(see figure 2, 4A, 4B). Wiegel et al further teaches mutations of Asp87 (GAC) to GLY (GGA), Tyr (TAC), Asn (AAC), Ile (ATC), Ile (ATT), Gly (GGC), Glu (GAG) (See figure 4A and 4B). Wiegel also teaches nucleotides of codon 85 can encompass GTT or GTG or GTA (see figure 2). Wiegel teaches codon 89 is ATC or ATT (see figure 2). The single nucleotide mutations taught by Wiegel demonstrate how altering one nucleotide can alter a codon and thus the amino acid.

With regards to claim 5, Wiegel also teaches the amplification of gyrA for the examination of QRDR mutations in bacteria (see pages11 line 19 to page 12 line 15)(claim 5). Wiegel also teaches and claims a nucleic acid probe to determine the quinoline resistance of E. coli GyrA (See claim 30 and table 4).

With regards to claims 9 and 10, Wiegel teaches the use of labels including: radioactive, enzyme, and fluorescent labeling (see page 10 lines 1 and 2).

However, Wiegel does not teach an array containing capture probes for all permutations of nucleotides for the codons at positions 87 and 83, in which the capture probes also account for possible mutations in codons 85 and 89.

Alberts et al, teaches all the possible combination of nucleotides for a codon (see figure 3-16, page 106).

However, with regards to claims 1-3, Chee et al (A) (WO 95/11995) teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and its codons with a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. The block-tiling array allows the interrogation of multiple nucleotide sites by use of multiple probe sets, which represent every permutation of nucleotides possible for a give sequence. Chee (A) teaches the determination of all possible combinations of nucleotides surrounding a SNP, allowing determination of all possible nucleic acid. Chee (A) teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). With regards to claim 6, Chee et al (A) teaches DNA fragmentation (see page 126, number 4), prior to contacting with capture probes.

Therefore, it would be prima facie obvious for the ordinary artisan to improve the method of detecting quinolone resistant bacteria taught by Wiegel with permutations of nucleotides resulting in different codons taught by Alberts and the block tiling array method of Chee to make a genus of 15-30 nucleotide probes with every possible

permutation in gyrA at codons 83 and 87. Probes of this length would necessitate the inclusion of codons 85 and 89 and their permutations, and would include a capture probe comprising the sequence of E.coli_GyA87A1 from table 1. The ordinary artisan would be motivated by the gyrA genetic variability taught by Wiegel in figures 2, 4A and 4B to construct an array of capture probes consisting of all possible permutations at codons 83, 85, 87, and 89 to detect all possible mutations of gyrA resulting in quinoline resistance in E.coli, because Chee (A) teaches simultaneous detection and quantification of multiple target sequences, resulting in identification of mutants associated with disease.

Response to Arguments

The response traverses the rejection. The response asserts that Weigel et al teaches quinolone resistance in Enterobacteriaceae and does not suggest quinolone resistance can be determined in E. coli by assessing mutational status at residues 83 and 87 (see page 6 of response filed on October 6, 2006).

This argument has been considered but is not convincing because the Weigel teaches, "E.coli revealed single mutations at codon 83 of gyrA associated with low levels of resistance and double mutations (codons 83 and 87) with high levels of resistance " (see page 18, lines 1-34). Weigel thus teaches mutations in E.coli gyrA at nucleotides corresponding to codons 83 and 87 does result in E.coli quinolone and motivation to examine both codons, because Weigel teaches mutations in both codons result in greater quinolone resistance. Therefore Weigel specifically teaches quinolone resistance in E.coli by assessing mutational status of residues 83 and 87.

The response further asserts Weigel does not teach all permutations of nucleotides for codons at positions 83 and 87 of gyrA and only teaches one mutant codon for residue 83 and 3 mutant codons for residue 87 (see page 6 of response filed October 6, 2006).

This argument has been considered but is not convincing because Weigel teaches multiple mutations of the gyrA at codons 83 and 87 (see figure 4 A and 4B) within additional organisms including: wild type codon ser83 (TCG) and mutant codons Leu (TTG), Thr (ACT), Thr (ACC), (Ser) AGC, Ser (TCC), Ile (ATC), Phe (TTC), Tyr (TAC), Ile (ATT), Arg (CGC), Arg (AGG), Arg (AGA)(see figure 2, 4A, 4B) and codon Asp87 (GAC) to GLY (GGA), Tyr (TAC), Asn (AAC), Ile (ATC), Ile (ATT), Gly (GGC), Glu (GAG), as previously cited. Weigel teaches mutations in all 3 nucleotide positions of the codons recited, result in altered amino acid sequences and quinolone resistance. The ordinary artisan would clearly be interested in analyzing E.coli for all possible mutations and combinations to assess quinolone resistance and would interrogate all 3 nucleotide positions of codons 83 and 87.

Chee specifically teaches a method for the simultaneous detection and quantification of multiple target sequences (see page 32, lines17-19), including closely spaced mutations by use of probes complementary to the corresponding positions in the reference sequence (see page 37, lines 1-8).

The ordinary artisan would have improved Weigel's screening method by use of Chee's multiple closely spaced interrogation site tiling array, because Chee teaches his arrays allow simultaneous detection and quatification of multiple target sequences. The

tiling array of Chee encompasses closely spaced mutations which facilitate rapid and effiecient analysis. Thus designing a tiling array using the closely spaced mutations of Wiegle would have facilitated the effiecient analysis of all the quinolone resistant strains.

The response further asserts Weigel is silent as quinolone resistance changes at residues 85 and 89 as referred to in claim 3 (see page 6 of response October 6, 2006).

This argument has been considered but is not convincing because claim 3 recites, "wherein the sequences R_1 and R_2 are designed such that known nucleic acid changes at amino acid position 85 and 89 are considered." Claim 3 thus does not require amino acid positions 85 and 89, are involved in quinolone resistance. Further the specification teaches mutations at 85 (GTT (val) to GTC (val)) and 89 (CGT (arg) to CGC (arg)) that do not alter the amino acid sequence (see page 12, table 2), nor does the specification teach these mutations result in quinolone resistance. Using the design of the tiling arrays with analyzes positions 5' and 3' of the mutations would necessarily analyze positions 85 and 89.

Moreover, Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8) to identify pathogenic microorganisms and mutations to such microorganism resulting in drug resistance (see page 19, lines 23-25). Chee thus reiterates the use of probes in one assay to allow detection of quinolone resistance.

Thus for the reasons above and those already of record, the rejection is maintained

10. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegel, Alberts, and Chee (A) as applied to claim 1-3, 5-6, and 8-10, and further in view of Chee

et al (B)(Science (1996), Volume 274, pages 610-614) and Routier (Nucleic Acids Research, (1999) volume 27, pages 4160-4166).

The teachings of Wiegel in view of Chee (A) and Alberts are set forth above. Wiegel in view of Chee and Alberts does not teach fragmentation of DNA to 40-60 nucleotides.

However, Chee (B) teaches fragmentation improves the uniformity and specificity of hybridization (see page 613 third column, lines 43 and 44). Routier teaches a method of fragmentation resulting in fragments of 10-40 nucleotides (see Figure 5).

Therefore it would be prima facie obvious for one of ordinary skill the art at the time of the invention to modify the method of Wiegel, Chee (A), and Alberts of the detection of gyrA mutants with the Routier method of DNA fragmentation wherein the fragments are 10-40 nucleotides. Routier teaches fragmentation with sizes of 10-40 nucleotides and Chee (B) teaches fragmentation improves uniformity and specificity of hybridization. The ordinary artisan would be motivated to optimize the size of fragments of the DNA prior to contacting with a microarray because Chee (B) teaches it improves specificity and uniformity of hybridization.

As stated in the MPEP, 2144.05 II, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)."

Response to Arguments

The response traverses the rejection. The response asserts, "The limitations of Weigel, Alberts and Chee (A) are discussed above. Neither of the additional references teach or suggest that quinolone resistance can be determined in

E. coli simply by assessing in a single assay the mutational status of residues 83 and 87. Thus, no combination of the cited references presages the claimed invention" (see page 7, October 6, 2006 response).

This argument has been considered but is not convincing for the reason cited above.

Thus for the reasons above and those already of record, the rejection is maintained.

Summary

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEANINE A. GOLDBERG
PRIMARY EXAMINER
12/18/06